The efficacy and safety of tranexamic acid use during radical cystectomy: A systematic review and meta-analysis

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ABSTRACT

Introduction: Radical cystectomy (RC) is the standard treatment for muscle-invasive bladder cancer (MIBC), but it is associated with substantial perioperative blood loss and high transfusion rates. Tranexamic acid (TXA), an antifibrinolytic agent, has demonstrated efficacy in reducing surgical blood loss across various specialties; however, due to a paucity of randomized controlled trials in the RC setting, its role remains uncertain. We conducted a systematic review and meta-analyses to synthesize the current evidence and provide a critical assessment of TXA use during RC.

Methods: Studies evaluating TXA during RC were identified through a comprehensive search of multiple databases up to November 2024. Primary outcomes included intraoperative and

perioperative blood transfusion rates and estimated blood loss. The secondary outcome assessed was thromboembolic events

Results: Five studies comprising 1736 patients were included. TXA did not significantly reduce estimated blood loss (MD: -85.56 mL; 95% confidence interval [CI] -191.13–20.02, p>0.05) or intraoperative transfusion rates (odds ratio [OR] 0.73, 95% CI 0.40–1.33, p>0.05); however, TXA was associated with a lower likelihood of perioperative transfusions (OR 0.56, 95% CI 0.32–0.97, p<0.05). Notably, TXA increased the risk of thromboembolic events (OR 2.05, 95% CI 1.15–4.65, p<0.05). Heterogeneity varied across analyses, with robotic-assisted RC underrepresented in the included studies.

Conclusions: This systematic review and meta-analysis revealed that, in patients undergoing RC, the use of TXA does not significantly reduce estimated blood loss or intraoperative transfusion rates. Moreover, TXA appears to be associated with an increased incidence of thromboembolic events, suggesting a potential pro-thrombotic effect. Based on these findings, its routine use in this context cannot be recommended, particularly when intended to reduce thromboembolic risk.

INTRODUCTION

Radical cystectomy (RC) is the gold-standard treatment for muscle-invasive bladder cancer (MIBC) and selected cases of high-risk non-muscle-invasive bladder cancer. While it offers curative potential, RC is associated with considerable perioperative morbidity, particularly due to significant blood loss and high rates of transfusion. Studies report transfusion rates ranging from 30% to 60%, with median blood loss frequently exceeding 1,000 mL [1–3].

Perioperative blood transfusion (PBT), although effective in managing acute conditions, has been associated with adverse outcomes, including a heightened risk of infections, immune modulation, and potentially worse oncologic outcomes, such as increased cancer recurrence rates [4,5]. These findings highlight the importance of implementing strategies to minimize blood loss and reduce the need for transfusions in patients undergoing RC.

Tranexamic acid (TXA), a synthetic antifibrinolytic agent, prevents the conversion of plasminogen to plasmin, stabilizing fibrin clots and reducing bleeding [6]. It is widely recognized as an effective agent in cardiac, orthopedic, and trauma surgeries, with evidence demonstrating its ability to reduce transfusion rates and blood loss without significantly increasing thromboembolic risks [7,8]. Although several studies have reported promising outcomes in reducing transfusion requirements and estimated blood loss, concerns persist regarding its efficacy in RC, thrombotic risks, and the variability in dosing regimens, limiting its routine adoption in this setting [9-11].

This study aims to assess the current evidence on the efficacy and safety of TXA in patients undergoing RC, providing a clearer understanding of its role and potential risks to guide clinical decision-making.

METHODS

Search strategy

This systematic review with comparative meta-analysis was performed following the Cochrane Collaboration Handbook for Systematic Review of Interventions [12] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines [13]. The protocol was prospectively registered in the PROSPERO international database (CRD42024604068).

The search strategy, detailed in the supplementary material, was designed to identify studies investigating the efficacy and safety of TXA during RC. Searches were conducted in the following databases up to November 2024: PubMed (MEDLINE), EMBASE (Excerpta Medica Database), Scopus, LILACS (Latin American and Caribbean Health Sciences Literature), ClinicalTrials.gov, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Brazilian Registry of Clinical Trials (ReBEC).

The search included both Medical Subject Headings (MeSH) and free-text terms for “Tranexamic Acid,” and “Radical Cystectomy” . Specific search terms used included:

(("Tranexamic Acid" OR "AMCA" OR "AMCHA" OR "t-AMCHA" OR "trans-4-(Aminomethyl) cyclohexane carboxylic Acid" OR "Cyklokapron" OR "Ugurol" OR "Transamin" OR "KABI 2161" OR "Amchafibrin" OR "Anvitoff" OR "Spotof" OR "Exacyl") AND ("Radical Cystectomy" OR "Cystectomy, Radical" OR "Radical Cystectomies"))

We manually reviewed the reference lists of included articles to identify additional relevant articles. Only studies published in English were considered.

Study screening and selection

Two independent reviewers conducted a thorough review of all retrieved records. Titles and abstracts were first screened to identify potentially eligible studies. The full texts of these studies were then reviewed in detail to confirm eligibility. Disagreements regarding inclusion or exclusion were resolved by consulting a third author.

Studies were eligible if they included adults (>18 years-old) patients undergoing RC, compared TXA use to either no TXA or placebo, and reported relevant outcomes. These outcomes included intraoperative and postoperative blood transfusion rates, estimated blood loss, the incidence of thromboembolic events, and postoperative complications. Randomized controlled trials (RCTs), prospective cohort studies, and retrospective comparative studies were eligible for inclusion. Editorials, narrative reviews, and non-comparative reports were excluded.

Data extraction and endpoints
Data extraction was performed using a structured Excel spreadsheet. Extracted information included patient demographics, study characteristics, intervention protocols, and clinical outcomes. The primary outcomes were intraoperative blood transfusion rates, postoperative blood transfusion rates, PBT, and estimated blood loss. Secondary outcomes included the incidence of thromboembolic events and pulmonary embolism (<90 days).

Quality assessment and risk of bias
The methodological quality of the included studies was evaluated independently by two authors using the Cochrane Collaboration's tools. For randomized controlled trials, the Risk of Bias 2 (RoB 2) tool was applied [14], while the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was used for prospective cohort studies [15].

Statistical analysis
For the comparative analyses presented in this systematic review, odds ratio (OR) with 95% confidence intervals and a random effects model were used for the pooling of data. Heterogeneity was assessed using I^2 statistics, where I^2>30% was considered significant. The statistical analysis was performed using R Studio (version 4.2.3, R Foundation for Statistical Computing, Vienna, Austria). Funnel plots, as well as Egger's regression test, were performed to assess publication bias for the primary outcome of this study [16]. Sensitivity analyses were performed to assess heterogeneity, systematically excluding one study at a time and recalculating the pooled results automatically with the Leave-One-Out heterogeneity test.

RESULTS

Literature screening

The literature search identified 52 records, which were screened by title and abstract. Of these, 22 were excluded as duplicates, and 23 were deemed irrelevant to the reviews aim. The full texts of the remaining 7 studies were assessed for eligibility, resulting in the exclusion of 2 studies due to inappropriate study design. Ultimately, 5 studies were included in the final analysis (2,6,9,17,18). Figure 1 presents the PRISMA flowchart summarizing the literature search and selection process.

Baseline characteristics of included studies
Five studies, encompassing a total of 1,736 patients were included. In most TXA administration protocols, an initial dose of 10 mg/kg was given at anesthetic induction, followed by a continuous infusion of 2 to 5 mg/kg/hr. The study by Egen et al. (2) was the only one that did not employ continuous infusion, based on the previous study by Devereaux et al. opting for a single 1 g dose administered half an hour before RC.

Only one study included patients undergoing robotic cystectomy, with the majority belonging to the TXA group (21.1% vs. 8.1%) (18). Regarding pathological staging, the proportion of patients with pT3 or pT4 disease ranged from 15.4% to 53% in the placebo group and from 18.7% to 35% in the TXA group. The percentages were similar between the placebo

and TXA groups, except in the study by Egen et al. (2), where the placebo group had a higher proportion of pT3/pT4 tumors (53%) compared to the TXA group (35%). A similar trend was observed for pathological lymph node involvement, with 25% of patients in the placebo group presenting nodal metastases, compared to 38% in the TXA group. The baseline characteristics of the included studies are shown in Table 1.

Quality assessment of the included studies

Regarding randomized studies, Breau et al. (17) conducted a double-blind, placebo-controlled randomized trial, demonstrating a low risk of bias according to the RoB2 assessment. The study's robust design enhances the reliability of its findings. In contrast, the study by Bibi et al. (9) presents significant methodological limitations. It lacks transparency regarding the randomization process and allocation method, omits crucial data on comorbidities and staging, and fails to comprehensively report all outcomes. The incompleteness of the reported endpoints further compromises its validity, making it a study with a high risk of bias.

Concerning non-randomized studies, the study by Egen et al (2) revealed notable disparities in patient characteristics between the cohorts. The group that received TXA had a higher proportion of ASA 1 patients (26% vs. 5%), while the control group had a greater prevalence of ASA 2 (57% vs. 46%) and ASA 3 patients (37% vs. 26%). Additionally, 54% of patients in the control group were staged as pT3/T4, compared to 34% in the TXA group, indicating a potential baseline imbalance in disease severity.

The study by Ahmed et al.(18) presents several sources of bias that may have influenced its outcomes. One key limitation is temporal bias, as the analysis included patients treated over a long period (1990–2021), introducing potential variations in surgical techniques and perioperative management. Additionally, the groups analyzed had distinct baseline characteristics, with the TXA group having fewer comorbidities, reflected in a lower median Charlson Comorbidity Index (2 [1–4] vs. 3 [2–8]) in the control group. Furthermore, robot-assisted surgery was more frequently used in the TXA group (20.1%) compared to the control group (8.1%), which may have influenced perioperative outcomes. Conversely, the study by Zaid et al. (6) featured a more homogeneous patient selection compared to other studies, resulting in a lower risk of bias and potentially more reliable findings. It is important to highlight that all retrospective studies attempted to adjust their analyses to minimize the influence of intrinsic discrepancies between groups. The quality assessments utilizing RoB2 and ROBINS I are shown in Figure 2.

Estimated blood loss

Four studies (6,9,17,18) evaluated the impact of TXA on estimated blood loss, involving a total of 784 patients in the TXA group and 879 in the placebo group. The pooled mean difference (MD), calculated using a random-effects model, was –85.56mL (95%CI: –191.13 to 20.02; $p>0.05$), indicating no statistically significant reduction in blood loss with TXA (Figure 3). Additionally, substantial heterogeneity was observed among the four studies ($I^2 = 75.9\%$,

p=0.005). In the leave-one-out sensitivity analysis, the study by Bibi et al. (9) contributed the most to heterogeneity. When this study was excluded, heterogeneity dropped to I^2=0%, but the overall result remained non-significant, showing no difference between groups (Supplementary Figure 1).

Intraoperative blood transfusions

The analysis of intraoperative blood transfusions included four studies (2,6,9,17), with a total of 351 patients in the TXA group and 796 patients in the placebo group. The pooled OR using a random-effects model was 0.73 (95% CI: 0.40 – 1.33, p > 0.05), indicating no statistically significant reduction in the need for intraoperative blood transfusions with TXA compared to placebo (*Figure 4*).

Heterogeneity was substantial (I^2=60.3%, p=0.05), indicating significant variability among the included studies. The study by Breau et al. (17) contributed the greatest weight (35.5%) and reported an OR of 1.22 (95% CI: 0.75–1.98), favoring the control group. A leave-one-out sensitivity analysis for intraoperative blood transfusion was conducted, confirming that the exclusion of individual studies does not significantly impact the estimated blood loss outcome. When omitting the study by Bibi et al.(9), heterogeneity dropped to I^2 = 0%, yet the overall result remained neutral, with no preference for either group (OR:0.98, 95%CI: 0.66–1.46) (Supplementary Figure 2).

Perioperative blood transfusions

Perioperative transfusion rates were assessed across four studies (2,6,17,18), including 779 patients in the TXA group and 1,194 in the placebo group. The pooled OR from the random-effects model was 0.56 (95%CI: 0.32 – 0.97; p<0.05), indicating that patients who received TXA had a 44% lower likelihood of requiring PBT (Figure 5).

High heterogeneity (I^2=82.6%, p<0.01) was observed, suggesting variability in study outcomes. The study by Ahmed et al. (18) strongly favored the TXA group, reporting an OR of 0.38 (95%CI: 0.29 – 0.50) and contributing the greatest weight (29.4%). Sensitivity analysis revealed that excluding the study by Breau et al. (17) reduced heterogeneity to its lowest level in this analysis (I^2=55.6%) and yielded a more pronounced effect, with an OR of 0.43 (95%CI: 0.28 – 0.67; p<0.01) (Supplementary Figure 3).

Figure 5. Comparative analysis of PBT between TXA and placebo groups in patients who underwent RC.

Postoperative thromboembolic events

Four studies (2,6,17.18), comprising 779 patients in the TXA group and 1224 in the placebo group, evaluated the risk of postoperative thromboembolic events. The pooled OR calculated using a random-effects model was 2.05 (95%CI:1.15 – 4.65, p<0.05), indicating a statistically significant difference between TXA and placebo (*Figure 6*).

Heterogeneity was low (I^2=0%, p=0.42), reflecting relatively consistent findings across the studies. The study by Ahmed et al. (18) carried the most significant weight (37.7%) and reported an OR of 1.73 (95%CI: 0.68 – 4.44).

Postoperative pulmonary embolism

Three studies (6,17,18) evaluated the effect of TXA on overall postoperative complications, including a total of 744 patients in the TXA group and 839 in the placebo group. The pooled OR using a random-effects model was 1.49 (95%CI:0.69 – 3.24, p>0.05), indicating no statistically significant difference between TXA and placebo (Figure 7). The heterogeneity was low between studies (I^2=0%, p = 0.97).

DISCUSSION

To our knowledge, this is the first systematic review with meta-analysis to investigate the use of TXA in patients undergoing RC. We analyzed a total of 1,736 patients and found no significant difference between TXA and placebo in estimated blood loss and intraoperative transfusion rates. However, patients who received TXA were less likely to require PBT and had a higher risk of thromboembolic events within 90 days.

The effect of TXA remains controversial, depending on the clinical context of its use. A study involving 9,535 patients undergoing noncardiac surgery, randomized to receive TXA (4,757 patients) or placebo (4,778 patients), demonstrated a lower likelihood of composite bleeding outcome events—defined as life-threatening bleeding, major bleeding, or bleeding into a critical organ—at 30 days in the TXA group (11). Similarly, a meta-analysis evaluating TXA treatment in patients undergoing hip fracture surgery found a significant reduction in intraoperative blood loss, overall blood loss, and transfusion rates (19,20).

Conversely, a systematic review of seven studies evaluating the efficacy and safety of TXA in managing lower gastrointestinal bleeding revealed heterogeneous effects. Another meta-analysis focusing on TXA use in spinal surgery similarly failed to demonstrate consistent benefits regarding blood loss and transfusion reduction (21). The authors suggested that variability in effect sizes and potential biases across studies may have influenced these outcomes. These findings further emphasize the complexity of TXA's hemostatic effects, which may differ based on the clinical context and patient population (21,22).

Our analysis yielded results consistent with those of Breau et al. (2024) (17) in the highest-quality double-blind, randomized controlled trial conducted to date on this topic. The study found no significant difference in estimated blood loss or transfusion rates. However, our meta-analysis demonstrated a lower PBT rate among patients receiving TXA. This finding was likely influenced by the large sample size of retrospective studies, particularly the study by Ahmed et al. (2024) (18), with 936 patients analyzed.

A more significant proportion of patients in the TXA group underwent robot-assisted surgery (21.1%) compared to the placebo group (8.1%). Given that robot-assisted RC has been

associated with reduced intraoperative blood loss and lower transfusion rates, this imbalance may have contributed to the observed difference (23).

Moreover, the Ahmed et al. (2024) (18) study reported a higher burden of comorbidities in the placebo group (Charlson Comorbidity Index median 3 [3-8]) compared to the TXA group (median 2 [1-4]). This discrepancy introduces a significant confounder, potentially influencing the observed benefit of TXA in reducing transfusion rates.

Regarding thromboembolic events, our analysis revealed that patients receiving TXA had twice the risk of developing thromboembolic complications compared to those in the placebo group. Most studies on general surgery have not demonstrated significant differences in thromboembolic risk with TXA use (24). Similar findings have been reported in plastic surgery cohorts (25) and in a meta-analysis encompassing 216 studies across multiple surgical specialties, which suggested that intravenous TXA, regardless of dosing, is not associated with an increased risk of thromboembolic events (26). However, RC is a prolonged pelvic surgery that involves extensive manipulation of pelvic veins during lymphadenectomy. Despite prophylactic measures, approximately 4.7% to 6% of patients experience postoperative deep vein thrombosis (27,28). This inherent thrombotic risk may amplify the prothrombotic effect of TXA in this specific surgical setting, explaining the observed differences between groups.

The limitations of this systematic review include the heterogeneity of the analyzed population, the scarcity of randomized controlled trials, and the variability in TXA infusion protocols among the limited number of studies available on this topic. Despite robotic-assisted RC becoming a routine practice in uro-oncology, only a single study in our analysis included data on robot-assisted procedures, and even then, in a minimal proportion of patients.

It is important to highlight that this meta-analysis included two RCT (9,17) and three observational studies (2,6,18), which mandates cautious interpretation of the findings—particularly regarding discordant outcomes. The observed increase in venous thromboembolic events associated with TXA use is supported by biological plausibility and signals from retrospective data; however, this association was not confirmed in the high-quality RCT(17). This discrepancy reinforces the need for further prospective well-designed trials to clarify the safety profile of TXA in the context of RC.

Moving forward, standardized protocols with larger cohorts of patients undergoing robotic-assisted RC are essential to contextualize the current evidence within contemporary surgical practice. This would help determine whether the limited impact of TXA on blood loss and transfusion rates observed in open cystectomy is replicated in the robotic-assisted setting. Additionally, these findings emphasize the need for individualized strategies for TXA administration in RC to optimize its potential benefits while mitigating risks.

CONCLUSIONS

This systematic review and meta-analysis revealed that, in patients undergoing radical cystectomy, the use of tranexamic acid (TXA) does not significantly reduce estimated blood loss or intraoperative transfusion rates. Moreover, TXA appears to be associated with an increased

incidence of thromboembolic events, suggesting a potential pro-thrombotic effect. Based on these findings, its routine use in this context cannot be recommended, particularly when intended to reduce thromboembolic risk.

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FIGURES AND TABLES

Figure 1. Prisma diagram.

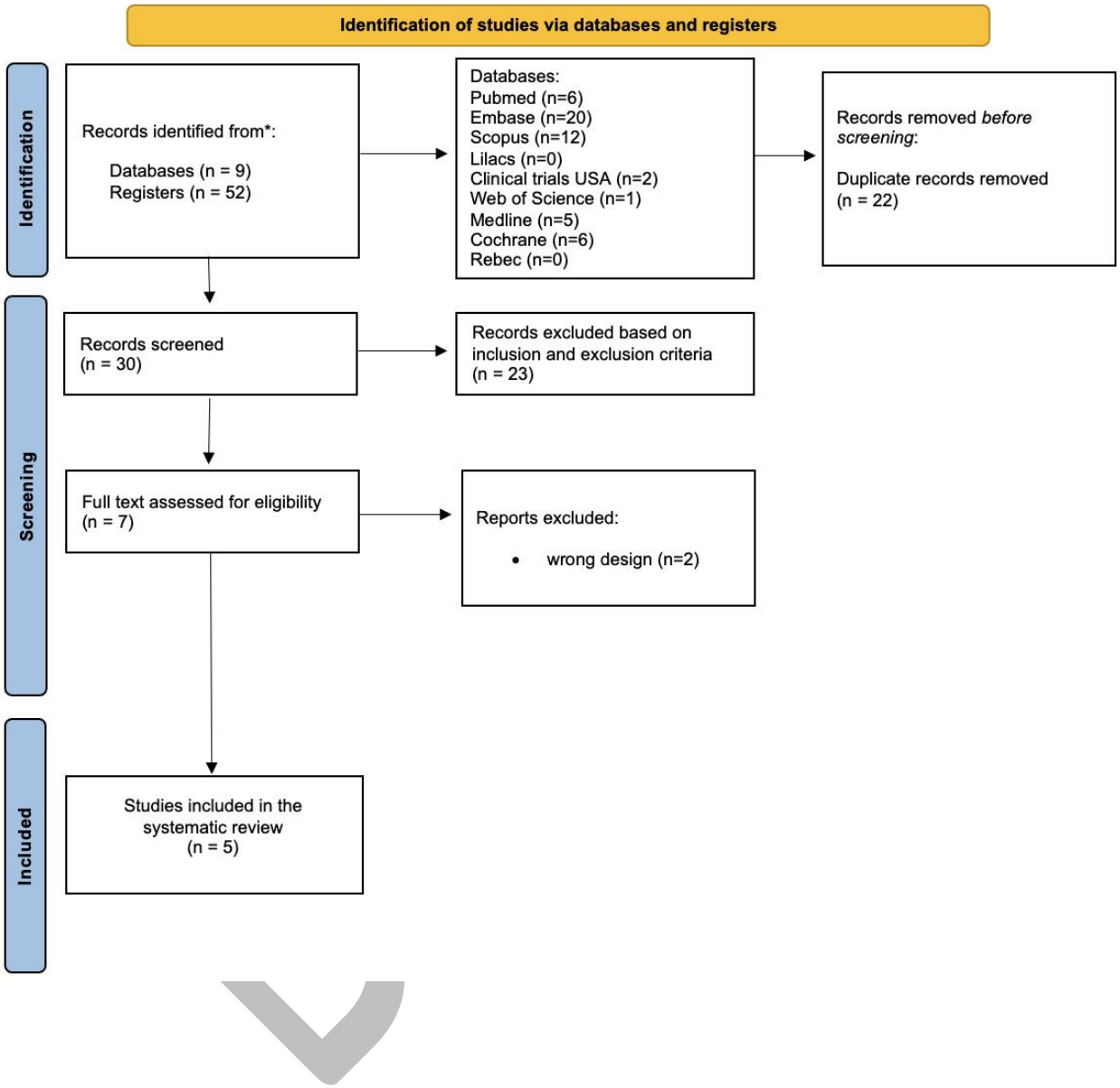
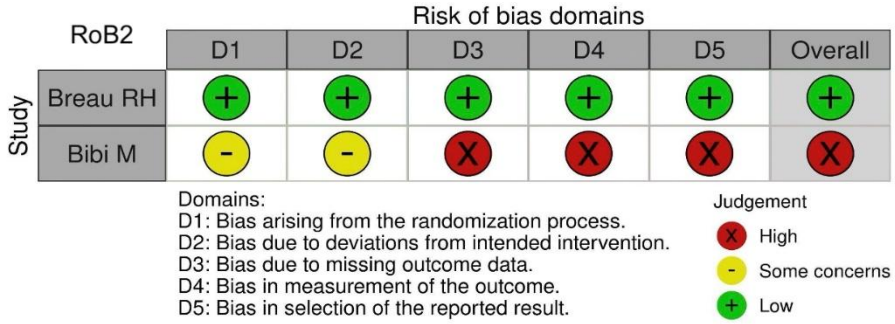


Figure 2. Risk of bias analysis.



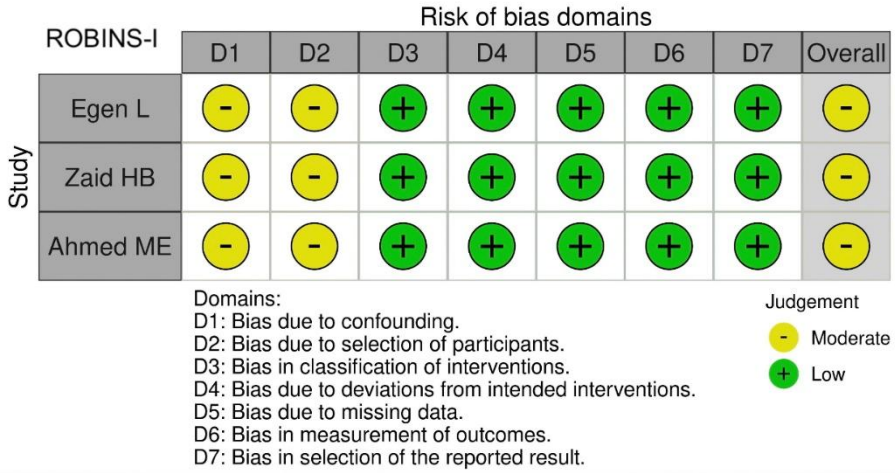


Figure 3. Mean difference in estimated blood loss (mL) between patients receiving tranexamic acid and placebo in patients who underwent radical cystectomy. CI: confidence interval; SD: standard deviation.

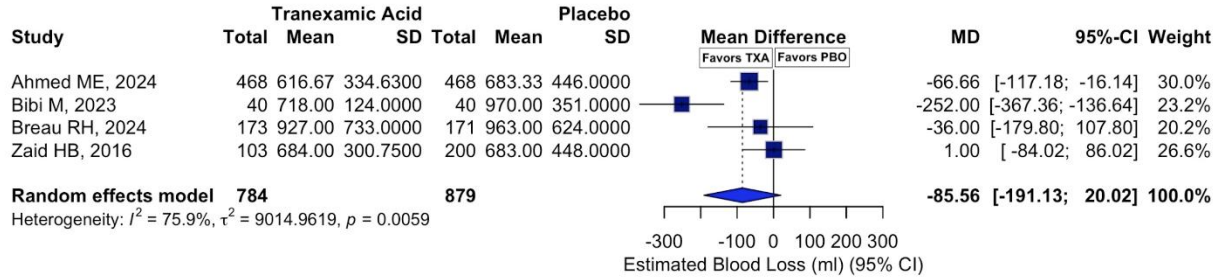


Figure 4. Comparative analysis of intraoperative blood transfusions between tranexamic acid and placebo groups in patients who underwent radical cystectomy. CI: confidence interval; OR: odds ratio.

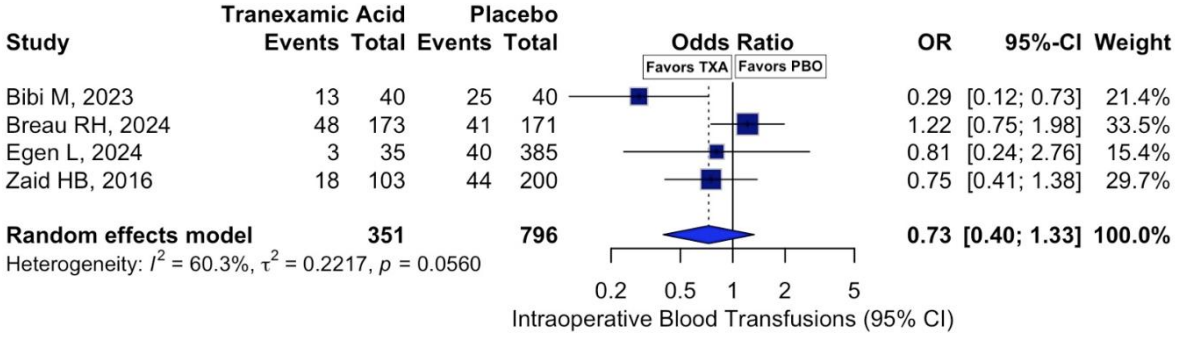


Figure 5. Comparative analysis of perioperative blood transfusions between tranexamic acid and placebo groups in patients who underwent radical cystectomy. CI: confidence interval; OR: odds ratio.

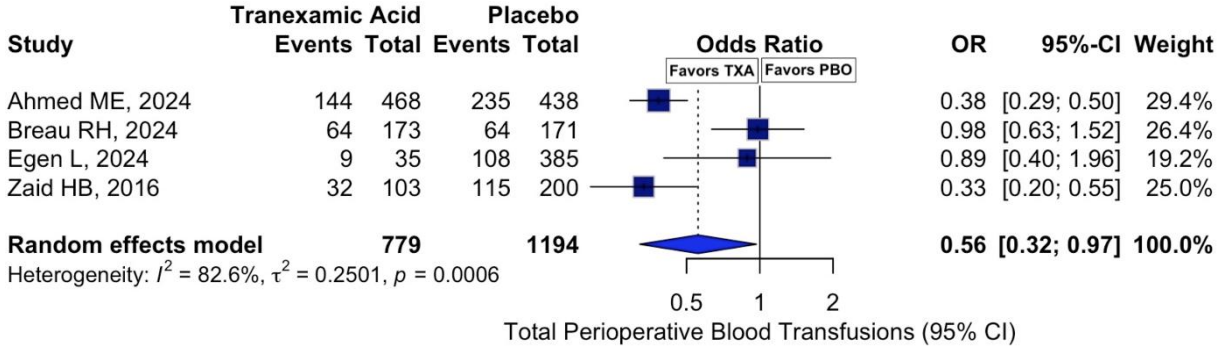


Figure 6. Comparative analysis of postoperative thromboembolic events in patients receiving tranexamic acid vs. placebo in radical cystectomy. CI: confidence interval; OR: odds ratio.

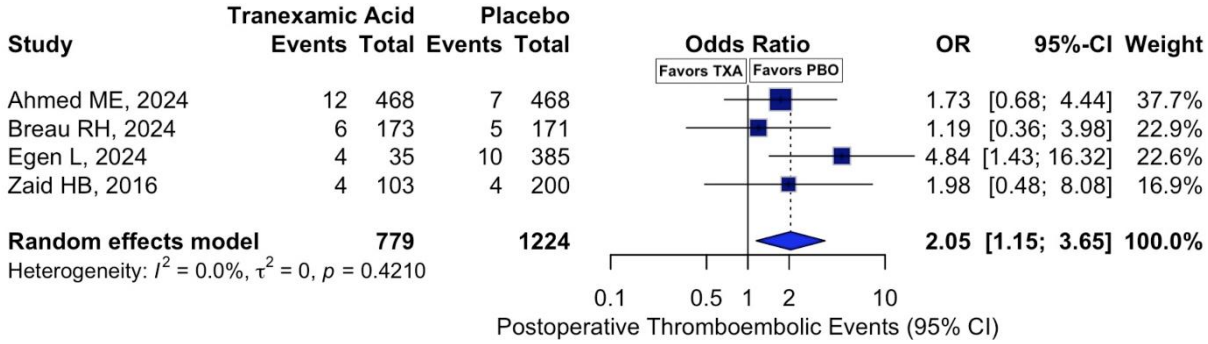


Figure 7. Comparative analysis for postoperative pulmonary embolism in patients receiving tranexamic acid vs. placebo in radical cystectomy. CI: confidence interval; OR: odds ratio.

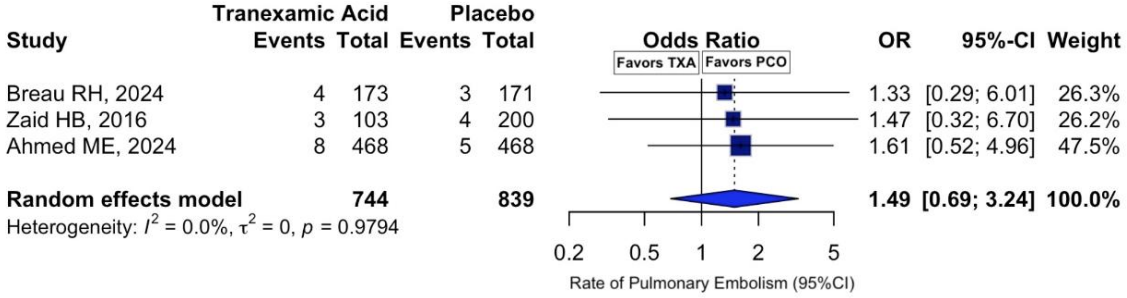


Table 1. Baseline characteristics of the included studies.

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Study	**Year**	**Country**	**Study design**	**Total of patients (No TXA/TXA)**	**TXA protocol**	**Robotic surgery, n (%)**		**Age (years)**		**>pT2, n (%)**		**pN+, n (%)**		**Primary endpoint**
						Non-TXA	TXA	Non TXA	TXA	Non-TXA	TXA	Non-TXA	TXA	
Egen	2024	Germany	Retro-spective	420 (385/35)	1g half an hour before RC	0	0	72 (±9)	68 (±10)	20 (53)	11 (35)	8 (25)	12 (38)	Perioperative blood transfusion
Zaid	2016	USA	Retro-spective	303 (200/103)	10 mg/kg of TXA over 20 minutes, a few minutes prior to surgical incision, followed by an infusion of 2mg/kg/hr	0	0	68.7 (61.7 –5.5)	69 (61.1–74.9)	58 (29)	29 (28.2)	29 (14.5)	15 (14.6)	Perioperative blood transfusion
Bibi	2023	Tunisia	RCT	80 (40/40)	10 mg/kg in bolus + 2 mg/kg/hr during the surgery	0	0	–	–	–	–	–	–	Perioperative estimate blood loss (<30 days)
Breau	2024	Canada	RCT	344 (173/171)	10 mg/kg 10 min before	0	0	68.2	69.9	27 (15.4)	33 (18.7)	36 (21.1)	37 (21.3)	Red blood cell transfusion

					the surgical incision + 5 mg/kg/hr for the duration of surgery (stopped ± 20 minutes from skin closure)			(62–76)	(63.8–74.6)					(<30 days)
Ahmed	38 (8.1)	USA	Retrospective	936 (468/468)	10 mg/kg in bolus + 2 mg/kg/hr during the surgery		94 (21.1)	65 (59–71)	69 (62–73)	103 (22)	103 (22)	66 (14.1)	66 (14.1)	Perioperative estimated blood loss, blood transfusion, and risk of venous thromboembolism (<30 days)